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FOREWORD

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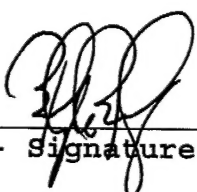
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Introduction

In 1996 we completed a population-based, cross-sectional/cohort telephone survey of 3,695 military personnel to compare the prevalence of self-reported symptoms and illnesses among military personnel either deployed, or eligible but not deployed, during the Gulf War (GW) (JAMA, 1997). The Iowa Gulf War Study was originally funded by the Centers for Disease Control and Prevention. Compared with non-GW military personnel, GW deployed military personnel reported a significantly higher prevalence of symptoms of a variety of conditions, although the frequency of *a priori* defined outcomes of depression, cognitive dysfunction, and chronic widespread pain were particularly elevated. The validity of these outcomes and the existence of a causal relationship between either military exposures or other risk factors and documented illness for most symptomatic GW veterans remains to be demonstrated.

This study, a series of case-validation and case-control studies nested within the previous population-based cohort study, should provide an estimate of the frequency of clinical illness. Because of the magnitude of the difference in self-report prevalence across deployment status, it is critical to explore and characterize the degree to which these groups exhibit cognitive deficits, depression, and chronic widespread pain upon clinical examination. The primary purpose of the current project is to compare the true rate of confirmed disease among samples of veterans deployed to the Gulf with and without these predefined conditions, versus the true rate of confirmed disease among samples of veterans not deployed, with and without these outcomes. We also plan to identify risk factors for each validated illness outcome of interest, including medical and family history, psychological and social factors, and occupational and environmental exposures in a series of nested case-control studies.

Year 4 of the grant has just been completed. Through September 2001, 578 subjects have been assessed, with a participation rate of 59%. Participation requires travel to Iowa City from any of the surrounding states for a full day in-person evaluation. Recruitment, assessment, data collection, data entry, and validation efforts are ongoing. We are also in the process of data editing, database linkage, and developing and programming of planned analyses. In the fall of 2001 the Department of Defense approved a two-year supplement and extension for this project. The supplement will allow an in-depth comparative analysis of the illness experience of Gulf War veterans from the US and the UK. The extension will ensure ample time to complete subject accrual and data analysis.

Past Year's Progress

Data Collection

At the end of September 2001 a total of 578 assessments had been completed. Table 1 and Appendix A provide detailed information on these subjects. In addition to our comprehensive interview and clinical evaluation, we have continued to perform blink reflex neurologic testing (as described in last year's report) on appropriate subjects. To date we have completed 44 (100 planned) of these tests. In addition, sampling, recruitment and assessments have begun in the neurophysiologic and neuromuscular substudies. At the end of September 2001 we had completed 9 neurophysiologic substudy assessments (of a planned total of 60), and 13 (of a planned 60) neuromuscular assessments. See Appendix B for a complete breakdown of progress on these neurologic tests.

Instruments

Appendix C presents a detailed list of instruments and assessments used in the study. We have made no additions to the main subject assessment in the past year. We have continued collecting data for the qualitative study component described in detail in last year's annual report. A total of 106 interviews using the revised version of our qualitative interview have been conducted thus far (coupled with 232 interviews using the earlier version of the interview). Data collection, transcription and preliminary coding are ongoing.

A great deal of time and effort was invested in developing the sampling plan and data collection instruments and procedures to ensure maximal yield from the neuromuscular and neurophysiologic assessments. We developed questionnaires for both substudies constituting a distinct subset of questions. These distilled substudy questionnaires assess current symptomatology and relevant related information. We also developed a neuromuscular reexamination form, a limited exam excerpted from our regular-visit exam, which our physician examiners are using to reassess specific neuromuscular items. In addition, we developed an exam form, which the examining neurologist is using for the neuromuscular exam. Appendix D presents these materials.

Characteristics of Subjects Assessed to Date

Through 30 September 2001, a total of 578 subjects had been assessed. In addition, 79 potential subjects have either scheduled a future appointment or have expressed interest in scheduling an appointment. Of those sampled, 403 have declined to participate. Currently a conservative participation rate is estimated at 59%. We are collecting structured information on the reasons for declining participation, reviewing these data on an ongoing basis to determine potential interventions to improve recruitment and participation. The main reasons given for declining are inability to travel to Iowa City due to the distance and work schedule. We have taken steps to address these concerns (see "Schedule" below) and facilitate participation.

Table 1. Subjects Assessed Through 30 September 2001 (n=578)

	Number	Percent
Deployment status*		
Deployed - GW	423	73.2
Non-deployed - GW	155	26.8
Military status*		
Regular military	177	30.6
National Guard/Reserve	401	69.4
Gender		
Male	509	88.1
Female	69	11.9
Race		
White	560	96.9
Black/other	18	3.1
Branch*		
Army	417	72.1
Air Force	32	5.5
Marines	78	13.5
Navy/Coast Guard	51	8.8
Rank*		
Enlisted	546	94.5
Officer	32	5.5
State of residence		
Iowa	524	90.7
Illinois	18	3.1
Missouri	11	1.9
South Dakota Minnesota	5	0.9
Nebraska	4	0.7
Wisconsin	9	1.6
Other	4	0.7
	3	0.5
Age in years (at assessment)		
Mean	39.7	
Std. Dev.	9.0	
Minimum	27.3	
Maximum	70.7	

* At time of original telephone survey

Among those evaluated to date, there are a total of 423 deployed subjects and 155 non-deployed subjects. Of the 578 subjects assessed, 357 are cases, while the remaining 221 are controls (i.e., did not meet the case definition for cognitive dysfunction, depression, or chronic widespread pain at 1995-1996 structured telephone interview).

Appendix A presents a breakdown of subjects assessed to date by outcome and deployment status. Table 1 shows descriptive data on these study participants.

Data Analysis/Publication Plans

Data collected as part of the ongoing study to address the primary hypotheses have yet to be presented. Due to concern about influencing enrollment, affecting the blinded assessments, and to avoid interim analyses (which could adversely affect study power), we have decided not to examine differences between cases and controls or across deployment status until subject accrual is complete. However, we continue to make progress operationalizing the project's analytical goals and have proceeded with the development of statistical programs to generate the primary results upon completion of data collection. We have also been actively planning the manuscripts from the study and developing summary tables and figures, as well as draft methods and results sections, in collaboration with our study investigators.

Aside from the primary hypotheses, multiple manuscripts, abstracts, presentations and national invited presentations have been developed by members of the research team that examine a variety of Gulf War-related research questions and utilize data from this study population. A list of these works is shown in Appendix E. Other analyses and manuscripts are either in development or being planned.

Personnel

The study is fully staffed. Two notable investigator changes are the additions of Paul Peloso, MD, MSc and Praful Kelkar, MD. Dr. Peloso is a rheumatologist/clinical epidemiologist with specific expertise in chronic widespread pain, studies of clinical guidelines and clinical evaluations. Dr. Kelkar is a neurologist and is actively guiding the neuromuscular substudy. Appendix F shows the personnel associated with the project.

Research Methods

Throughout the past year we have held weekly meetings with key project staff and investigators. These meetings provide a forum for group discussion of myriad issues related to the study, including recruitment/study management and data analysis issues.

In anticipation of completing the data collection phase of the study and intensifying the data analysis phase, we have been working to have our databases, documentation and analytical programs in place. In doing so, when the final subjects finish the assessment, we can immediately begin analyzing the data. We are in the midst of verifying the code for constructed variables and testing the programs for the planned analyses using a small subset of the data. This helps to identify programming and coding problems and further refine the statistical methodology. Work on this front is progressing well, and we anticipate no lag between study phases. We are also planning and conducting a series of analyses that were not outlined in the grant that we feel are appropriate and scientifically important.

Laboratory evaluations have been completed as planned on all 217 subjects meeting the case definition for chronic widespread pain. Algorithms have been developed to identify subsets participants for further neurophysiologic and neuromuscular studies based on the results of objective testing conducted during their visit to Iowa City. These algorithms were developed in collaboration with Drs. Thoru Yamada, Mark Ross, Praful Kelkar and Joseph Barrash from the Department of Neurology, Dr. Paul Peloso from the Department of Internal Medicine and Dr. James Torner, our neuroepidemiologist. We have applied these algorithms and the identified individuals are currently being recruited for and participating in the neurophysiologic and neuromuscular substudies. After careful review of the planned neurologic assessment, we have also expanded the detail and complexity of the assessment, based on further input from our neurologic and neuromuscular diagnostic experts.

As noted earlier, last year we implemented blink reflex testing on a subset of subjects, at the suggestion of our consultants. This relatively noninvasive neurophysiologic test has been used in other studies to quantify conduction latency in subjects who have been exposed to environmental contaminants. In our study, data gathered using this test will be used to assess for and quantify any neuropathy in subjects who may exhibit cognitive dysfunction. This testing evaluates the nerve pathways that carry signals through the facial nerve, trigeminal nerve, and to the brainstem. We plan to conduct the blink reflex test in a total of up to 100 subjects: 10 deployed and 10 nondeployed subjects from each of the four *a priori* case definition categories that include cognitive dysfunction (CD alone, CD + depression, CD + chronic widespread pain, and CD + depression + chronic widespread pain), as well as 10 deployed and 10 nondeployed control subjects. As noted earlier, 44 blink reflex assessments have been completed, to date. Appendix B presents detailed breakdowns of the subjects who have completed blink reflex testing.

We are using the facilities of the University of Iowa Health Care's (UIHC) General Clinical Research Center (GCRC) for the assessments. These facilities provide an optimal clinical research setting for the project and allow a "subject-centered" research assessment. Instead of transporting subjects to different parts of the hospital to undergo the various facets of the assessment, subjects are centrally located in the GCRC throughout their visit. Subjects are provided with lunch in the GCRC cafeteria and, if desired, can spend the night in a GCRC inpatient room. In addition, an experienced GCRC nurse obtains vital signs and performs phlebotomy.

In addition to the primary data that will be generated in this project, we have been working to obtain and link secondary data to assess pre-deployment health status variables, as well as post-deployment data associated with our research subjects. We have been working actively with the DoD's Defense Manpower Data Center (DMDC) and the Center for Health Promotion and Preventive Medicine (CHPPM) to secure access to other clinical and military data relevant to this project. These data include variables collected at enlistment and throughout an individual's military career. This information will help in a variety of analyses, including the assessment of pre-existing states/conditions, aid in controlling for pre-deployment health status, and as a validity check for a variety of self-reported variables.

Research Subjects and Sample

Subjects were sampled from participants of the original Iowa Gulf War study (n=3,695). To limit the pool of subjects to those most likely to participate (given the need for travel to Iowa City for an in-person evaluation), the pool was subset to include only telephone survey participants whose last known address was in Iowa or a bordering state. The total number of eligible subjects in these states, referred to as "the surrounding region", is 2,464. Appendix G presents the number of eligible subjects broken down by exposure status and symptomatology based on the study's three *a priori* outcomes.

Each subject was categorized into one of eight categories, reflecting the seven possible combinations of the three *a priori* outcomes of interest (Table 2), as well as a category for those who do not meet the criteria for any of the three outcomes. A "case" is an individual who, based on the telephone survey, meets the criteria for one or more of the following *a priori* outcomes: cognitive dysfunction, chronic widespread pain, and/or depression. A control subject is an individual who did not meet the definition for any of these three *a priori* outcomes, based on the telephone survey data. Subjects are also categorized reflecting whether or not they were deployed to the Arabian Gulf Theater during the GW era. The resulting number of potential subjects in each group is shown in Table 2.

As Table 2 shows, among the cases, deployed subjects outnumber non-deployed subjects for all but one of the categories ("depression only" is the exception). To yield maximum precision in the estimate of the false positive rate of symptom reporting, deployed to non-deployed subjects were sampled in an approximate 2 to 1 ratio. Because of the relatively small numbers of non-deployed cases, we are attempting to recruit all the non-deployed cases in any of the seven combinations of outcomes. We have randomly selected twice this number of deployed cases. If fewer than twice as many deployed as non-deployed subjects are available for a given outcome combination, all the deployed subjects for that stratum will be recruited.

There were two exceptions to the 2 to 1 ratio of deployed to nondeployed. First, we included all 85 of the deployed cases meeting the case definition for cognitive dysfunction. Cases who met the definition for cognitive dysfunction, but not the criteria for the other two study conditions are of particular importance in order to optimally characterize this group, which is of great clinical interest. Therefore, the decision was made to include in the sample the 25 deployed cases with only cognitive dysfunction and who would not have been selected by strict adherence to the planned 2 to 1 ratio. Secondly, all 58 of the deployed cases meeting the *a priori* case definition for both cognitive dysfunction and chronic widespread pain were included in the sample. Strict adherence to the 2 to 1 ratio would have lead to only 18 deployed cases sampled with this combination of conditions. In order to fully characterize those with reports of cognitive dysfunction, it was decided to include all 58 deployed cases meeting the case definition for this outcome combination.

Utilizing the sampling strategy outlined above, the original sampling pool included 1064 military personnel. This was intentionally conservative, based on anticipated

participation among subjects interviewed by telephone in 1995-96 who would need to be located and brought to Iowa City approximately five years later for in-person evaluation. As in our original study, we planned to draw the sample in stages, based on conservative estimates of effectiveness in subject tracking, locating and recruitment. We have also found that recruitment of control subjects is more difficult than that of case subjects, since control subjects are more often reluctant to miss work for the travel involved. A second-stage sample was planned and implemented after nine months of subject accrual. We analyzed participation by the original sample, based on the original stratification variables included: age, sex, race, military branch, military status, and rank. Based on the distribution of characteristics in the study population, participation rates within strata, and theoretical and epidemiologic considerations, it was decided to stratify the sample on the basis of military branch (army and marines vs. air force and navy/coast guard), regular military vs. guard/reserve, and officer vs. enlisted.

The second-stage sample analysis determined the number of new control subjects that needed to be added to each of 17 strata comprising the demographic categories above (all potential subjects defined as cases were included in the first-stage sample). For each stratum, we projected the number of sampled individuals necessary to allow the stratum, given the percentage of unavailable subjects from the first-stage sample and projected conversion rate for unavailable subjects, to meet its target number of completed assessments.

Women constitute a small proportion of the overall study population and were not oversampled in the original cohort study. To maximize statistical power in analyses involving women, since this is one of the first conflicts that women have served in "war fighter" roles, during the second-stage of sampling it was decided to oversample women. Given the small overall number of women in this population (approximately 9%) and the relative difficulty locating them (name changes are the primary challenge), all eligible women were included in the sample. Although this will likely result in a lower participation rate than expected, we felt it important to characterize this group as fully as possible. This sampling strategy yielded a total of 266 control subjects to be added to the recruitment pool (139 deployed women and 127 nondeployed women).

The appropriate number of subjects in each stratum was selected randomly. Cases are also of central importance in order to adequately characterize illness among deployed individuals and identifying their associated risk factors. To maximize precision when addressing these questions, it was decided to sample cases to controls at an approximately 2 to 1 ratio. As seen in Table 2, this sampling plan would yield a maximum of 257 non-deployed cases, and 471 exposed cases, for a total of 728 cases.

Table 2. Total Cases and Controls Available for Assessment, Desired Sample Sizes, and Completed Subjects by *A Priori* Outcome Group Combinations*

	<i>A Priori</i> Outcome Groups	Not Deployed			Deployed			Total		
		Total	Target	Complete	Total	Target	Complete	Total	Target	Complete
Cases	Cognitive Dysfunction, Chronic widespread pain, and Depression	28	28	12	82	56	45	110	84	57
	Cognitive Dysfunction and Chronic widespread pain	9	9	5	58	58	36	67	67	41
	Cognitive Dysfunction and Depression	32	32	9	65	64	32	97	96	41
	Cognitive Dysfunction only	30	30	7	85	85	49	115	115	56
	Chronic widespread pain and Depression	20	20	10	30	30	17	50	50	27
	Chronic widespread pain Only	87	87	30	130	130	62	217	217	92
	Depression Only	51	51	16	48	48	27	99	99	43
	Subtotal of cases	257	257	89	498	471	268	755	728	357
Controls	None of the three conditions†	919	100	66	791	200	155	1,710	300	221
Totals		1,176	357	155	1,289	671	423	2,465	1,028	578

*Neurocognitive evaluation to be completed on approximately 100 deployed controls and 100 non-deployed controls.

*Note: data complete as of September 30, 1999, based on geographic location at last known address (time of survey, 1995-96). We have recently obtained updated address information from the Internal Revenue Service through the National Institute of Occupational Safety and Health (NIOSH) with assistance of DoD. This updated address information provided updated addresses for selected subjects we have been unable to locate and expanded our pool of eligible subjects with a last known address in Iowa or the surrounding states.

Subject Locating and Tracking

A major consideration for this study is locating and contacting potential research subjects. Five years have passed since the telephone survey, and a large number of subjects have relocated in the meantime. Once the initial sample for the present study was identified, the following steps were taken to maximize the probability of locating and contacting the largest possible number of selected subjects. First, an introductory letter was sent to the subjects' last known address. The letter discussed the current study and instructed subjects on how to contact the project via a toll-free number should they have questions, or if they would like to set up an appointment. Included with this letter was a return postcard to allow subjects to make any necessary corrections to their address and phone number, and to list the best times for telephone contact. If a subject returned the postcard with contact instructions, follow-up was made per those

instructions. If no specific callback date was noted, contact was made as soon as possible after receiving the postcard.

In many cases, the original introductory letter was returned as undeliverable. Sometimes a label would be affixed to the envelope listing the subject's current address, and in these cases a new letter was issued to that address. More commonly, a letter was returned with no current address listed. In this setting, several Internet locating services were used to try to determine the subject's current address. If this failed to produce any leads, a directory assistance call was placed to the last known city. If this yielded no listing for the subject of interest, a telephone call was placed to the permanent contact person the subject listed in the previous telephone survey.

The permanent contact person has been a valuable tool for locating a large number of subjects. In instances where the permanent contact person is not available, or is not able or willing to provide updated information on a potential subject, the search for the subject has been outsourced to ChoicePoint (formerly Equifax), a credit agency search firm that specializes in locating individuals. Thus far we have sent two batches of names to ChoicePoint, comprising approximately 140 subjects. ChoicePoint was able to supply good contact information for half of these individuals (69 of 140).

At the end of grant year 3, we obtained IRS address information on our sample. We greatly appreciate the assistance of LtC. Michael Leggieri, LtC. Rick Riddle, and Maj. Gen. Parker at DoD for their repeated assistance in this endeavor. This address information has been a valuable aid for tracking down a large number of subjects who otherwise would have been unlocatable. In many instances, the IRS address was out of date, but generally the address was recent enough to make a cold trail warm. Given a relatively recent address, our search algorithm has proven effective.

Schedule

Recruitment for the main study and the substudies is ongoing, and is planned to continue through December 2001. Recruitment for the main study is getting increasingly difficult, as the majority of the subjects interested in participation (individuals who are most eager to participate, for whom travel is easy, etc.) have already been assessed.

As noted above, we have been systematically collecting and reviewing data concerning why subjects find it difficult or to participate decline participation altogether. To address these issues, we began offering Saturday appointments every weekend possible. We also now offer increased reimbursement for travel for those traveling more than 2 hours to Iowa City. We have worked to further increase flexibility in assessment times by offering later start times. Several shift workers have been able to participate in the study by beginning their assessment in the late morning or in the afternoon, instead of our usual 8:00 am start time.

Several additional steps have been taken to boost recruitment. First, the aforementioned IRS address search allowed us to resume active recruitment of the over 200 subjects that had been unlocatable. The more recent address information also allowed us to identify a handful of eligible subjects who had moved back to Iowa or the Midwest since the time of the telephone interview in 1995-96.

We are in the process of recontacting subjects who expressed an interest in participating but were unable to schedule an appointment at the time of contact. This is routinely done for subjects who are unable to schedule an appointment at the time of our initial call. Notably, the availability of Saturday appointments often allows us to convert a contingent of subjects who declined based on their unavailability during the week. To date we have converted (completed or scheduled an assessment) 14 of 37 such subjects, a 30% success rate. There are 190 more of these subjects to resolve, and recruiting as many as possible will be a top priority for the remainder of the study.

We also developed and mailed a newsletter to distribute to participants in the original telephone survey (presented in last year's annual report). The newsletter provides background on the current study, includes comments from study participants regarding their satisfaction with the current evaluation, and demonstrates our research productivity and participation on national committees and in national presentations with the data being provided. Our goal was to help inform potential subjects about the study, enhance subject tracking and generate some interest among potential subjects. We are currently planning the development of a study webpage, to further facilitate the communication of study results to subjects and the public.

Data Management

Study data are double entered on an ongoing basis. Multiple steps are routinely taken to ensure data accuracy and quality. First, all case report forms and questionnaires are reviewed by research personnel prior to the subject leaving for the day. Second, all data are being entered on electronic forms programmed in Microsoft Access, with built-in range and consistency checks. For example, if a specific item only has a valid range of 1 through 5, the form is set up to accept input only within this range. The forms are also designed to closely resemble the original instruments from which the data are coded. To help ensure the accuracy of data entry, two different data entry personnel are entering all the data separately. The second entry is compared with the first, and any discrepancies are resolved. Discrepancies that cannot be easily resolved, i.e., that are due to an ambiguous response by the subject or something else beyond a simple keystroke error, are reviewed by the study coordinator and, if necessary, by the principal investigator. If the response is still unclear, the study coordinator contacts the subject for clarification.

Data entry has been in progress since the subject assessment phase of the project began. To date, data for each assessed subject have been entered once, and the second data entry is nearly complete. We have found a very low rate of data entry errors, which have reduced to a negligible rate over time.

Conclusion

The project is fully staffed and subject accrual and assessment are ongoing. Recruitment and assessment processes are being constantly assessed for opportunities to increase efficiency and effectiveness. We plan to continue subject accrual and assessments through CY 2001. We are actively planning data analyses and manuscript development in order to efficiently execute the study's data analysis phase, once subject accrual is complete. Data entry is keeping pace with completed assessments, and analysis programs are being written and tested in an effort to expedite the analysis phase. Also, in an effort to maximize the efficient use of the rich database that is being developed as part of this study, the research team is actively developing interim analyses that will lead to papers and presentations of interest even while subject accrual is in progress. We have also been productive in presenting and publishing results of our research in important scientific journals and at national meetings.

Appendix A. Completed Assessments Broken Down by *A Priori* Outcome and Deployment Status (Assessments completed through 9/30/01)

Cognitive Dysfunction

	Deployed	Not Deployed	Total
Symptomatic ¹	162	33	195
Not Symptomatic	261	122	383
	423	155	578

Depression

	Deployed	Not Deployed	Total
Symptomatic	121	47	168
Not Symptomatic	302	108	410
	423	155	578

**Chronic
widespread pain**

	Deployed	Not Deployed	Total
Symptomatic	160	57	217
Not Symptomatic	263	98	361
	423	155	578

By Illness Combinations: Total Assessments Completed to Date

	CD	Dep	Fibro	CD, Dep	CD, Fibro	Dep, Fibro	CD, Dep, Fibro	No Illness	Total
Deployed	49	27	62	32	36	17	45	155	423
Not Deployed	7	16	30	9	5	10	12	66	155
Total	56	43	92	41	41	27	57	221	578

¹ For each outcome, refers to self-reported symptomatology based on the 1995-96 telephone survey

Appendix B: Neurologic Substudy Testing Progress: Blink Reflex, Neurophysiologic, and Neuromuscular Testing

Blink Response Test*

	Deployed	Nondeployed	Total
Cases: CD	3	1	4
Cases: CD, Dep	6	2	8
Cases: CD, Fibro	6	0	6
Cases: CD, Dep, Fibro	6	2	8
Controls	11	7	18
	32	12	44

*Goal: 10 Assessments in each cell: 50 deployed+ 50 nondeployed = 100 total assessments

Neurophysiologic Assessment**

	Complete	Remaining	Total
Deployed Cases, documented deficit	6	19	25
Deployed Cases, inadequate effort	1	24	25
Nondeployed controls	2	8	10
	9	51	60

**Brainstorm Auditory Evoked Potential (BAER) and Somatosensory Evoked Potential Assessment (SEP) in subset of deployed cases with documented neurocognitive deficit by objective testing, deployed cases judged by psychologist consensus to have put forth inadequate effort, and nondeployed controls

Neuromuscular Assessment***

	Complete	Remaining	Total
Cases	7	23	30
Control	6	24	30
	13	47	60

***Nerve Conduction Studies (NCV), Needle Electromyography (EMG) and Repetitive Nerve Stimulation will be conducted on a subset of 30 deployed cases with symptoms of muscle weakness and 30 nondeployed controls

Appendix C. Data Collection Instruments

1. NEUROPSYCHOLOGICAL BATTERY

Test/Item	Abilities assessed
Background Interview	Academic/neurologic history
WAIS-R Similarities	Verbal intellect
WAIS-R Block Design	Nonverbal intellect, visuoconstruction
WAIS-R Digit Span	Concentration, immediate memory span
WAIS-R Digit Symbol	Nonverbal learning, visuomotor speed
NART-R	Premorbid intelligence
COWA	Expressive language, sustained attention
Rey AVLT	Verbal learning and memory
AVLT-Repeated Delay	Exaggeration
BVRT	Immediate visual, memory, exaggeration
RMT	Verbal memory, visual memory, exaggeration
Stroop Test	Response inhibition, concentration
Trail Making Test	Visual scanning, visuomotor speed, cognitive shifting
Starry Night Test	Reaction time, sustained visual attention
Grooved Pegboard Test	Manual dexterity, visuomotor integrity
MMPI-2	Psychological status, exaggeration

NART-R = National Adult Reading Test-Revised; COWA = MAE Controlled Oral Word Association Test; Rey AVLT = Rey Auditory Verbal Learning Test; BVRT = Benton Visual Retention Test; RMT = Warrington Recognition Memory Test; MMPI-2 = Minnesota Multiphasic Personality Inventory-2.

2. MENTAL HEALTH EXAMINATION

Instrument	How Administered	Assesses
SCID-IV	rater	Axis I disorders
GAS	rater	Global function
BLSQ	self-report	Life Stress
Mississippi Scale	self-report	PTSD symptom severity, effects
SPS	self-report	Social support
Barsky Amplification Scale	self-report	Amplification
ASI	self-report	Amplification; Hypochondriasis
Whiteley Index	self-report	Amplification; Hypochondriasis
MASQ	self-report	Mood and Anxiety
SNAP	self-report	Personality

SCID-IV = Structured Clinical Interview for DSM-IV Non-Patient Version; GAS = Global Assessment Scale; BLSQ = Brief Life Stress Questionnaire; SPS = Social Provisions Scale; MASQ = Mood and Anxiety Symptom Questionnaire; SNAP = Schedule of Nonadaptive and Adaptive Personality

3. PATIENT EVALUATION

Instrument	How Administered	Evaluation
History and Physical form	Clinician	History and Physical
Review of Systems form	Clinician	Review of Systems
Family History form	Clinician	Family History
Disability and Distress Rating	Clinician	Physical Disability and Psychological Distress
SF-36	Self-report	Health Status
Health Utilities Index	Self-report	Health Status, Utility Measure
Dartmouth COOP Charts	Self-report	Health Status, Health Functioning
10 cm. Visual Analog Pain Scale	Self-report	Current Pain
Occupational Exposure questionnaire	Self-report	Occupational Exposure

Appendix D. Neurologic Substudy Materials: Questionnaires and Exam Forms

INFORMED CONSENT DOCUMENT
FOR SUBJECTS PARTICIPATING IN NEUROMUSCULAR EXAMINATIONS

Project Title: **Illness Among Persian Gulf War Veterans: Case Validation Studies**

Investigator(s): Bradley N. Doebbeling, MD, MSc; Joseph Barrash, PhD; Don Black, MD; Caroline Carney Doebbeling, MD; Thoru Yamada, MD; Praful Kelkar, MD; Paul Peloso, MD; Robert Woolson, PhD; John Holman, MA; Tomoko Sampson, MPH; Jane Anderson

PURPOSE

This study involves research. The purpose of the research is to learn more about problems with the muscles and nerves in military personnel reporting symptoms and medical problems. In total, approximately 60 persons will be invited to participate in the neuromuscular examination described below. Your participation in this study is entirely voluntary. If English is not your first language, we can provide a translator for you.

You are being invited to participate in this research because you served in the United States Armed Forces during the period of the Persian Gulf War and participated in a telephone survey conducted by the University of Iowa Persian Gulf Study Group (September 1994 - May 1995). The same investigators who conducted the telephone survey are in charge of this study. Participation in this study will last approximately three hours.

PROCEDURES

If you agree to participate and are eligible for this study, the following will happen:

1. You will be asked to participate in repetitive nerve conduction studies (RNS) and electromyography (EMG). Nerve conduction studies, repetitive nerve stimulation, and electromyography are standard diagnostic tests performed to evaluate nerve and muscle function among patients. The results of these tests may give the physician information that can be used to help determine if a patient has a nerve or muscle disorder.
 - a. RNS tests how well signals travel along a nerve and can help find the cause of abnormal nerve function. Signals are made to travel along the nerve by applying a series of seven small electric pulses to the nerve at one site through an electrode placed on the skin and recording the response at a different place along the nerve. The nerve's response is picked up by a recording instrument and then is measured by the physician or technologist performing the test. If the intensity of the stimulus is too uncomfortable, the intensity of the stimulus can be decreased. Several nerves may need to be tested depending on the type of problem.
 - b. For the electromyogram (EMG), the physician inserts a small needle into a muscle to record the electrical activity of the muscle. The electrical activity of the muscle is fed into the recording instrument and the physician then analyzes it by looking at a signal on the scope and listening to the sounds the activity makes through the speaker. This test can help determine if there are abnormalities in the muscle or the nerve going to it.

RISKS

The possible risks associated with participating in this research project are as follows. During the RNS test, you may feel a short, mild tingling feeling caused by the small electric pulse. There may be mild discomfort during the EMG when the needle is inserted into the muscle. The needles are discarded after use to prevent the transmission of infections. There is no foreseeable risk of physical injury associated with these tests.

BENEFITS

There may be no direct personal benefit to you for participation in this study. Knowledge gained from this study may benefit others and enhance the general knowledge about health consequences of the Persian Gulf War. This information may help identify risk factors for illness that may be prevented during future military service.

COSTS AND COMPENSATION

You will not be charged for any tests that are being performed strictly for the purposes of this study. You will be paid for time and inconvenience involved in participating in the research in the amount of \$75. Payment will be pro-rated if you withdraw before the research is completed. For example, if you complete half of the study, you will be paid \$26. Payment will be mailed to you in the form of a check as soon as possible after you leave the University of Iowa. You also will be provided free overnight room and board in the Clinical Research Center if you travel 100 miles or more to reach the University of Iowa.

CONFIDENTIALITY

Records of participation in the research project will be maintained and kept confidential to the extent permitted by law. However, federal government regulatory agencies and the University of Iowa Institutional Review Board may inspect and copy a subject's records pertaining to the research, and these records may contain personal identifiers. All data will be maintained using coded identification numbers; paper records will be kept in a locked file cabinet in a secure location, and electronic data will be protected with such measures as passwords and firewalls. In the event of any report or publication from this study, the identity of subjects will not be disclosed. Results will be reported in a summarized manner in such a way that subjects cannot be identified.

RESEARCH RELATED INJURY

In the event of research related injury, medical treatment is available at the University of Iowa Hospitals and Clinics. No compensation for treatment of research related injury is available from the University of Iowa unless the injury is proven to be the direct result of negligence by a University employee. The cost of treatment for any research-related illness or injury will be paid for by the sponsor, the Department of Defense, to the extent that these costs are not covered by the research subject's medical or hospital insurance carrier.

VOLUNTARY PARTICIPATION

Your participation is voluntary. No penalty or loss of benefits to which you are entitled will occur if you decide not to participate. You may discontinue participation at any time without penalty or loss of benefits to which you are entitled.

QUESTIONS

Questions are encouraged. If there are any questions about this research project, please contact: Dr. Bradley N. Doebbeling, The University of Iowa, Iowa City, Iowa, 52242, phone 319/356-8556. Questions about the rights of research subjects or research related injury may be addressed to the Human Subjects Office, 300 College of Medicine Administration Building, The University of Iowa, Iowa City, Iowa, 52242, (319) 335-6564.

.....

Subject's Name (printed): _____

(Signature of Subject)

(Date)

INVESTIGATOR STATEMENT

I have discussed the above points with the subject or the legally authorized representative, using a translator when necessary. It is my opinion that the subject understands the risks, benefits, and obligations involved in participation in this project.

(Signature of Investigator)

(Date)

Subject ID _____

Iowa Gulf War Study Case Validation Study
Neuromuscular Verification Form

Date ____/____/____

Completed by: _____ (Neurologist's Initials)

Limited Physical Exam

Muscle strength		R*	L*	Comments
Neck flexors	N A	___/5	___/5	
Neck extensors	N A	___/5	___/5	
Deltoid	N A	___/5	___/5	
Biceps	N A	___/5	___/5	
Finger flexors	N A	___/5	___/5	
Finger extensors	N A	___/5	___/5	
Interossei	N A	___/5	___/5	
Grip strength	N A	___/5	___/5	
Iliopsoas	N A	___/5	___/5	
Quadriceps	N A	___/5	___/5	
Tibialis anterior	N A	___/5	___/5	
Gastrocnemius	N A	___/5	___/5	

*Range from 0 to 5 (normal)

Abnormal muscle group findings should be listed in EMG section to be tested.

Reflex rating	Right	Left	
Bicep jerk	0 1* 2* 3* 4*	0 1* 2* 3* 4*	
Tricep jerk	0 1* 2* 3* 4*	0 1* 2* 3* 4*	
Knee jerk	0 1* 2* 3* 4*	0 1* 2* 3* 4*	
Tendo-achilles	0 1* 2* 3* 4*	0 1* 2* 3* 4*	
Plantar	Up Down	Up Down	

0=absent; 1=decreased; 2=nl; 3=increased but w/o clonus; 4=markedly increased w/ clonus

☐ Check here if subject has *medical history* that is related to neuromyopathy. (Please describe in Comments.).

☐ Check here if subject is on *medication* that may cause neuromyopathy. (Please describe in Comments)

Please direct any questions to:

Praful Kelkar, MD
Investigator – Neurology
Iowa Gulf War Study
Phone: 6-8776
Pager: 2077

or

Brad Doebbeling, MD, MSc
Principal Investigator
Iowa Gulf War Study
SE625 GH
Phone: 6-8556
Pager: 3585

or

John Holman, MA
Study Coordinator
Iowa Gulf War Study
C-34 Annex
Phone: 4-9096
Pager: 7791

Nerve Conduction Studies

(Check when completed)

- ☐ Median motor
- ☐ Median sensory
- ☐ Peroneal motor
- ☐ Sural sensory
- ☐ Median F wave
- ☐ Peroneal F wave

Repetitive Nerve Stimulation

- ☐ Spinal Accessory – Baseline
- ☐ Spinal Accessory – 3 Minute

Comments:

Needle Electromyography (EMG)

Required Muscles Tested (on same side as NCS):

- ☐ Deltoid
- ☐ Tibialis anterior

Additional muscles tested (from exam*):

- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____

* Abnormal muscle strength findings must be tested by EMG in addition to the required muscles.

Completed by: RZ DJ BD

Has a doctor ever told you that you have:	
Depression	Y
Problems with thinking abilities	Y
Fibromyalgia	Y
Chronic fatigue syndrome	Y
Multiple chemical sensitivity	Y
Can you tell me about any medical conditions that have been diagnosed by a doctor over the last three years? (do not read list – if positive, specify timing, onset, treatment, and other details at right)	
Neurologic	
Recurrent headaches	Y
Migraines	Y
Neuralgia or neuritis	Y
Amnesia	Y
Narcolepsy	Y
Traumatic Brain Injury/Concussion (specify)	Y
Endocrine	
Hyperthyroidism	Y
Hypothyroidism	Y
Diabetes	Y
Renal	
Kidney (renal) disease (specify)	Y
Frequent urinary tract infections	Y
Arthritis	
Low back pain	Y
Muscle or tendon disorder (specify)	Y
Chronic fatigue syndrome	Y
Arthritis or rheumatism	Y
Derm	
Eczema	Y
Psoriasis	Y
Other dermatitis (specify)	Y
Disease of the hair or scalp (specify)	Y
Skin cancer	Y
Psych	
Post-traumatic stress disorder	Y
Anxiety disorder (specify below)	Y
Alcohol abuse	Y
Substance abuse	Y
Other psychiatric disorder (specify below)	
Inf Dis	
HIV/AIDS	Y
Autoimmune	
Systemic Lupus Erythematosus	Y
Cancer	
Any Cancer (specify)	Y

[illegible]

Subject ID: _____

☐ Check here if subject has *medical history* that is related to neuromyopathy. (Please describe in Comments)

☐ Check here if subject is on *medication* that may cause neuromyopathy. (Describe in Comments)

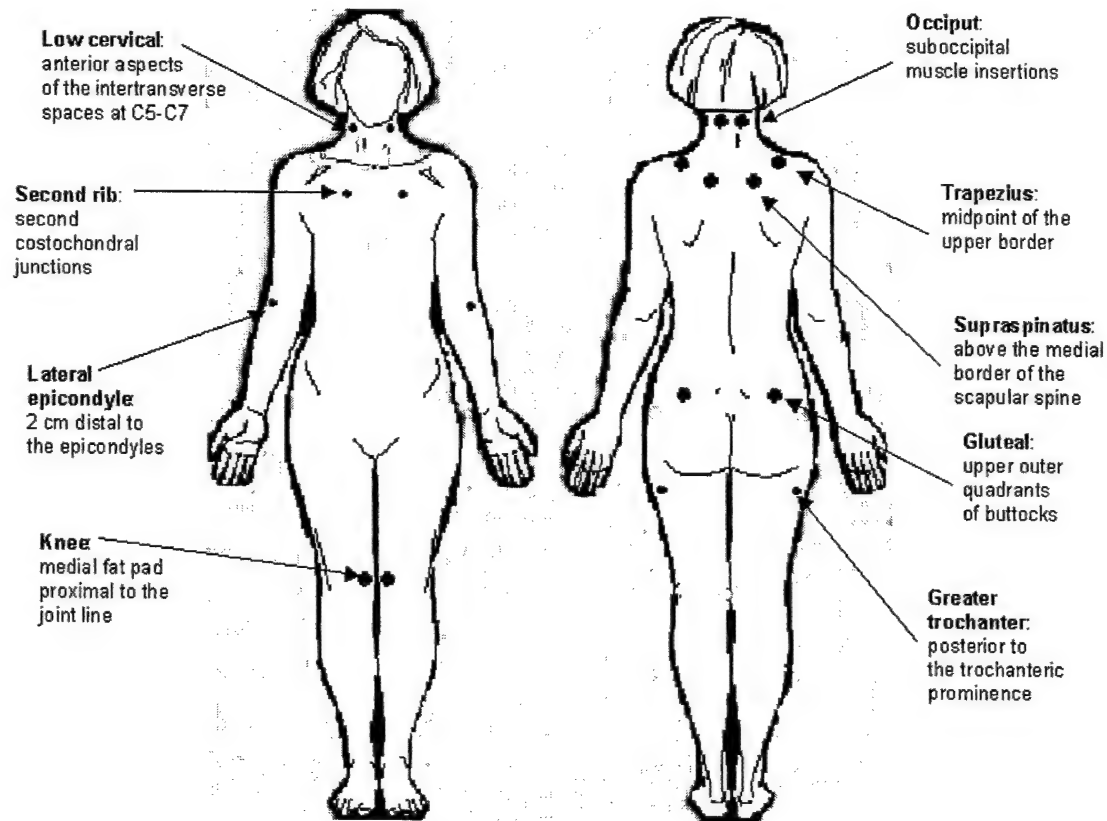
Limited Physical Exam

Muscle strength		R*	L*	Comments
Neck flexors	N A	___/5	___/5	
Neck extensors	N A	___/5	___/5	
Deltoid	N A	___/5	___/5	
Biceps	N A	___/5	___/5	
Finger flexors	N A	___/5	___/5	
Finger extensors	N A	___/5	___/5	
Interossei	N A	___/5	___/5	
Grip strength	N A	___/5	___/5	
Iliopsoas	N A	___/5	___/5	
Quadriceps	N A	___/5	___/5	
Tibialis anterior	N A	___/5	___/5	
Gastrocnemius	N A	___/5	___/5	
*Range from 0 to 5 (normal) Abnormal muscle group findings should be listed in EMG section to be tested.				

Reflex rating	Right	Left	
Bicep jerk	0 1* 2* 3* 4*	0 1* 2* 3* 4*	
Tricep jerk	0 1* 2* 3* 4*	0 1* 2* 3* 4*	
Knee jerk	0 1* 2* 3* 4*	0 1* 2* 3* 4*	
Tendo-achilles	0 1* 2* 3* 4*	0 1* 2* 3* 4*	
Plantar	Up Down	Up Down	
0=absent; 1=decreased; 2=nl; 3=increased but w/o clonus; 4=markedly increased w/ clonus			

Musculoskeletal	Normal/ Abnormal		Comments
Tender point exam (manual testing)	N A	# tender points	
Tender point exam (dolorimeter, if used)	N A	# tender points	

Location of FMS tender points:



Comments:

Iowa Gulf War Study Case Validation Study
Neuromuscular Sub-study Questionnaire

Symptoms and Conditions

In the past FOUR WEEKS have you had persistent or recurring problems with ...		No	A little bit	Moderately	Quite a bit	Very much
1	...pain or aches in more than one joint	0	1	2	3	4
2	...joint stiffness	0	1	2	3	4
3	...muscle tension, aches, soreness, or stiffness	0	1	2	3	4
4	...feeling tired	0	1	2	3	4

		Yes	No
5	During the past year did you have fibromyalgia or fibrositis?	1	2

Muscle Pain

In the past FOUR WEEKS have you been distressed by...		No	A little bit	Moderately	Quite a bit	Very much
6	... pain above the waist	0	1	2	3	4
7	... pain below the waist	0	1	2	3	4
8	... pain on the right side of your body	0	1	2	3	4
9a	... pain on the left side of your body	0	1	2	3	4

9b	Have you had any overall body pain, which includes pain in your arms and legs, back, and both sides of your body, during the past year? This pain would occur almost every day and would have lasted 3 months or longer. During the past year, did you have overall body pain like this	No	Yes
----	---	----	-----

If NO to question 9b, GO TO question 10

9c	(if YES to 9b) In what month and year did this first begin?	____/____ Mo. Yr.
----	---	----------------------

9d	We would like you to rate the level of pain you had during the past 24 hours. Think of a scale from 0 to 10. A 0 means there is no pain and a 10 means that the pain is the worst you have ever had. How would you rate the worst overall body pain you have had in the past 24 hours	_____
----	--	-------

9e	How would you rate the least overall body pain the last 24 hours?	_____
----	--	-------

10. Current Pain

Please rate the overall amount of pain you currently feel by drawing a line on the scale presented below:

Pain as bad as it could be |-----| No pain

Limitations Due to Health Problems

	Does your health now limit you in these activities that you might do during a typical day? If so, how much?	Not at All	A little bit	A lot
11	Vigorous activities	3	2	1
12	Moderate activities	3	2	1
13	Lifting or carrying groceries	3	2	1
14	Climbing several flights of stairs	3	2	1
15	Climbing one flight of stairs	3	2	1
16	Bending, kneeling or stooping	3	2	1
17	Walking more than a mile	3	2	1
18	Walking several blocks	3	2	1
19	Walking one block	3	2	1
20	Bathing or dressing yourself	3	2	1

INFORMED CONSENT DOCUMENT

FOR SUBJECTS PARTICIPATING IN NEUROPHYSIOLOGIC EXAMINATIONS

Project Title: **Illness Among Persian Gulf War Veterans: Case Validation Studies**

Investigator(s): Bradley N. Doebbeling, MD, MSc; Joseph Barrash, PhD; Don Black, MD; Caroline Carney Doebbeling, MD; Thoru Yamada, MD; Praful Kelkar, MD; Paul Peloso, MD; Robert Woolson, PhD; John Holman, MA; Tomoko Sampson, MPH; Jane Anderson

PURPOSE

This study involves research. The purpose of the research is to learn more about problems with the nerves that affect thinking ability in military personnel reporting symptoms and problems. In total, approximately 60 persons will be invited to participate in the neurophysiologic examination described below. Your participation in this study is entirely voluntary. If English is not your first language, we can provide a translator for you.

You are being invited to participate in this research because you served in the United States Armed Forces during the period of the Persian Gulf War and participated in a telephone survey conducted by the University of Iowa Persian Gulf Study Group (September 1994 - May 1995). The same investigators who conducted the telephone survey are in charge of this study. Participation in this study will last approximately three hours.

PROCEDURES

If you agree to participate and are eligible for this study, the following will happen:

You will be asked to participate in two neurophysiologic tests - brainstem auditory evoked potentials (BAEPs) and somatosensory evoked potentials (SEP). Evoked potentials evaluate the function of the nerve pathways that carry signals through the spinal cord, vision pathways, and hearing pathways. Nerve signals are produced in these nerves by applying small electric pulses to the nerves of the legs or arms, by pulses of light to the eyes, or by clicks of sound to the ears. The nerve's response is picked up from the skin over the surface of the spinal cord or the head. The results of these tests may give the physician information which can be used to help determine if a patient has a neurologic disorder.

For both the BAEP and SEP surface electrodes are placed over your scalp, neck, back, and extremities to record electrical impulse along the nervous system. For the BAEP, you will be asked to wear an ear phone. Several clicks to the ear produce the needed auditory stimulation. This test lasts about 20 to 30 minutes.

For the SEP, you will receive repeated electrical stimulations to your extremities (arms and legs) which cause small muscle twitches. In total, the SEP test takes about 20 minutes for each leg and arm.

RISKS

There is minimal discomfort involved with these tests. During the SEP test, you may feel a short, mild twitching feeling caused by the small electric pulse. There is no foreseeable risk of physical injury.

BENEFITS

There may be no direct personal benefit to you for participation in this study. Knowledge gained from this study may benefit others and enhance the general knowledge about health consequences of the Persian Gulf War. This information may help identify risk factors for illness that may be prevented during future military service.

COSTS AND COMPENSATION

You will not be charged for any tests that are being performed strictly for the purposes of this study. You will be paid for time and inconvenience involved in participating in the research in the amount of \$75. Payment will be pro-rated if you withdraw before the research is completed. For example, if you complete half of the study, you will be paid \$26. Payment will be mailed to you in the form of a check as soon as possible after you leave the University of Iowa. You also will be provided free overnight room and board in the Clinical Research Center if you travel 100 miles or more to reach the University of Iowa.

CONFIDENTIALITY

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RESEARCH RELATED INJURY

In the event of research related injury, medical treatment is available at the University of Iowa Hospitals and Clinics. No compensation for treatment of research related injury is available from the University of Iowa unless the injury is proven to be the direct result of negligence by a University employee. The cost of treatment for any research-related illness or injury will be paid for by the sponsor, the Department of Defense, to the extent that these costs are not covered by the research subject's medical or hospital insurance carrier.

VOLUNTARY PARTICIPATION

Your participation is voluntary. No penalty or loss of benefits to which you are entitled will occur if you decide not to participate. You may discontinue participation at any time without penalty or loss of benefits to which you are entitled.

QUESTIONS

Questions are encouraged. If there are any questions about this research project, please contact: Dr. Bradley N. Doebbeling, The University of Iowa, Iowa City, Iowa, 52242, phone 319/356-8556. Questions about the rights of research subjects or research related injury may be addressed to the Human Subjects Office, 300 College of Medicine Administration Building, The University of Iowa, Iowa City, Iowa, 52242, (319) 335-6564.

.....

Subject's Name (printed): _____

(Signature of Subject)

(Date)

INVESTIGATOR STATEMENT

I have discussed the above points with the subject or the legally authorized representative, using a translator when necessary. It is my opinion that the subject understands the risks, benefits, and obligations involved in participation in this project.

(Signature of Investigator)

(Date)

Iowa Gulf War Study Case Validation Study
Neurophysiological Patient Interview

Medical Conditions

	Has a doctor ever told you that you have:		Date Onset
1	Depression	<input type="checkbox"/>	
2	Problems with thinking abilities	<input type="checkbox"/>	
3	Fibromyalgia	<input type="checkbox"/>	
4	Chronic fatigue syndrome	<input type="checkbox"/>	
5	Multiple chemical sensitivity	<input type="checkbox"/>	

Other Neurological Outcomes

Please circle responses.

- 6a. Have you ever had any other neurologic condition such as seizures, a stroke, or an injury in which you were knocked out or became very confused?

Yes No

If Yes, go to 6b. If No, go to 7a.

- 6b. What happened (in the most severe injury or event)?

- 6c. Was there any loss of consciousness? Yes No

TBI (=1) Seizures (=2) CVA (=3) Brain surgery (=4) Other (=5) _____

- 6d. How many times (Estimate if necessary)? _____

- 6e. When (was the most severe injury)?

Mo/Yr

- 6f. When (was the most recent injury)?

Mo/Yr

- 6g. Were you seen in a hospital or clinic for this condition?

Yes

No

Subject ID _____
No _____

6h. Have you had a second neurologic condition? Yes

If Yes, go to 6h. If No, go to 7a

6i. What happened (in the second most severe injury or event)?

6j. Was there any loss of consciousness? Yes No

TBI (=1) Seizures (=2) CVA (=3) Brain surgery (=4) Other (=5) _____

6k. How many times (Estimate if necessary)? _____

6l. When (was the most severe injury)? _____

Mo/Yr

6m. When (was the most recent injury)? _____

Mo/Yr

6n. Were you seen in a hospital or clinic for this condition? Yes No

7a. Since the Gulf War, have you had any periods of significant problems with thinking abilities—
problems that you didn't used to have? Yes No

If Yes, go to 7b. If No, go to 8a.

7b. Are you still experiencing those problems? Yes No

7c. What kinds of problems have you had? _____

Memory	Yes	No
Attention/concentration	Yes	No
Language	Yes	No
Reasoning/comprehension	Yes	No
Perceptual/sensory	Yes	No
Psychomotor	Yes	No

7d. Looking back, when did these difficulties begin? _____

Mo/Yr

7e. Has the difficulty improved, stayed the same, or gotten worse over time? (Please circle.)

Better

Same

Worse

7f. Would you or others say the difficulty has interfered with your functioning?

Yes No

Subject ID _____

8a. Have you ever had any significant increases in alcohol or drug use since you last saw us?

Yes No

If Yes, go to 8b. If No, STOP HERE.

8b. How much alcohol have you been drinking? _____

Neuropathologically significant ETOH abuse: Yes No

8c. Which drugs have you have started using more? _____

8d. How frequently? _____

8e. For how long? _____

Neuropathologically significant drug abuse: Yes No

Iowa Gulf War Study Case Validation Study
Neurophysiological Sub-study Questionnaire

Symptoms and Conditions

In the past FOUR WEEKS have you had persistent or recurring problems with ...

	No	A little bit	Moderately	Quite a bit	Very much
1 ...your memory		0	1	2	3
2 ...forgetfulness		0	1	2	3

In the past FOUR WEEKS have you...

	No	A little bit	Moderately	Quite a bit	Very much
3 ...had difficulty comprehending/understanding		0	1	2	3
4 ...had problems feeling confused or disoriented		0	1	2	3
5 ...had difficulty understanding what you read		0	1	2	3
6 ...had problems thinking clearly		0	1	2	3
7 ...had slips of the tongue when speaking		0	1	2	3
8 ...experienced difficulty concentrating		0	1	2	3

In the PAST MONTH have you ...

	No	A little bit	Moderately	Quite a bit	Extremely
9 ...had problems with forgetfulness (like forgetting where you put things or forgetting appointments)	0	1	2	3	4
10 ...had any difficulty comprehending or understanding what others are saying to you	0	1	2	3	4
11 ...had problems with feeling confused or disoriented in place or time (feeling confused about where you are, who is around, or not knowing what day it is)	0	1	2	3	4
12 ...had difficulty understanding what you read, even if you are paying attention to what you're reading	0	1	2	3	4

	No	A little bit	Moderately	Quite a bit	Very much
13 In the past four weeks did you have any amnesia or severe memory loss		0	1	2	3
14 During the past year, did you have any amnesia or severe memory loss		0	1	2	3

Appendix E. Recent Manuscripts and Presentations

Peer-Reviewed Papers Published or In Press:

Black, D.W., Doebbeling, B.N., Voelker, M.D., Clarke, W.R., Woolson, R.F., Barrett, D.H., and Schwartz, D.A. Quality of life and health service utilization in a population-based sample of military personnel reporting multiple chemical sensitivities. *J. Occup. Environ. Med.* 41(10):928-933, 1999.

Black, D.W., Doebbeling, B.N., Voelker, M.D., Clarke, W.R., Woolson, R.F., Barrett, D.H., and Schwartz, D.A. Multiple Chemical Sensitivity Syndrome: Symptom Prevalence and Risk Factors in a Military Population. *Arch. Intern. Med.* 160:1169-1176, 2000.

Doebbeling, B.N., Clarke, W.R., Watson, D., Torner, J.C., Woolson, R.F., Voelker, M.D., Barrett, D.H., and Schwartz, D.A. Is There a Persian Gulf War Syndrome? Evidence from a Large, Population-based Survey of Veterans and Nondeployed Controls. *Am. J. Med.* 108(9):695-704, 2000.

Sadler, A.G., Booth, B.M., Nielson, D., and Doebbeling, B.N. Health-related Consequences of Physical and Sexual Violence: Women in the Military. *Obstet. Gynecol.* 96:473-480, 2000.

Zwerling C, Torner JC, Clarke WR, Voelker MD, Doebbeling BN, Barrett DH, Merchant JA, Woolson RF, and Schwartz DA. Self-reported postwar injuries among Gulf War veterans. *Public Health Rep* 115:346-349, 2000.

Sadler AG, Booth BM, Cook BL, Torner JC, and Doebbeling BN. The Military Environment: Risk Factors for Women's Nonfatal Physical Assaults. *J. Occup. Environ. Med.* 43:325-334, 2001.

Doebbeling BN, Jones MF, Hall DB, Woolson RF, Clarke WR, Crumley T, et al. Methodological Issues in a Population-based Health Survey of Gulf War Veterans. *J. Clin. Epidemiol.* (In press), 2001.

Voelker, M.D., Saag, K.G., Schwartz, D.A., Chrischilles, E., Clarke, W.R., Woolson, R.F., and Doebbeling, B.N. Health-related Quality of Life among Gulf War Era Veterans. *Am. J. Epidemiol.* (In press), 2001.

Reviews, Editorials, Letters to the Editor:

Doebbeling BN, Clarke WR, Watson D, Torner JC, Woolson RF, Voelker MD, Barrett DH, and Schwartz DA. Will we solve the Gulf War Syndrome puzzle by population surveys or clinical research? [author's reply] *Am J Med.* 109:745-48, 2000.

Abstracts:

Doebbeling, B.N., Rohrer, J.E., Woolson, R.F., Torner, J.C., Saag, K.G., Merchant, J.A., Bentler, S., and Schwartz, D.A.: Health Services Utilization among Persian Gulf War and Activated Non-deployed Veterans. Annual Meeting of the American Public Health Association, Indianapolis, IN, p. 123, November 11, 1997.

Doebbeling, B.N., Woolson, R.F., Torner, J.C., Merchant, J.A., Barrett, D., Polzer, J.P., and Schwartz, D.A.: Self-reported Illness Following Service in the Persian Gulf: Multiple Medical Conditions. Annual Meeting of the American Public Health Association, Indianapolis, IN, p.5, November 10, 1997.

Voelker, M., Doebbeling, B.N.: Predictors of Mental Health Service Utilization Among Persian Gulf War Veterans. Abstracts of the 1997 International Conference on Health Policy Research: Methodologic Issues in Health Services and Outcomes Research. Boston, MA, December 1997.

Zwerling, C., Torner, J.C., Clarke, W.R., Voelker, M.D., Doebbeling, B.N., Barrett, D.H., Merchant, J.A., Woolson, R.F., and Schwartz, D.A.: Traumatic Injury Among Gulf War Era Veterans: An Analysis of the Iowa Persian Gulf War Study. 31st Annual Meeting of the Society for Epidemiologic Research, Chicago, IL, June 24-26, 1998.

Carney, C.C., Allen, J., Clarke W; Schwartz, D.A., Woolson, R., Barrett, D., and Doebbeling, B.N.: Gender Differences in Health Status in a Population-Based Sample of Military Personnel Deployed or Activated, Not Deployed to the Persian Gulf. 45th Annual Meeting of the Academy of Psychosomatic Medicine, Psychosomatics, November 1998.

Voelker, M.D., Torner, J., Woolson, R., and Doebbeling, B.N. Symptomatology Associated With Self-Perceived Health Decline among Gulf War Veterans and Era Controls. Abstracts of the Federal Investigators Annual Meeting on Persian Gulf War Illness, Washington, DC, June 23-25, 1999.

Simms, L. J., & Watson, D. Exploratory Factor Analysis of PTSD Symptoms in Two Military Samples. Abstracts of the 107th Annual Convention of the American Psychological Association, Boston, MA, August, 1999.

Sadler, A.G., Booth, B.M., Cooke, B.L., and Doebbeling, B.N. Military Occupational and Environmental Risk Factors for Rape: An Assessment by Era of Service. Abstracts of the 4th Federal Investigators Annual Meeting on Persian Gulf War Illness Research, Washington, DC, June 23-25, 1999.

Sadler A., Booth, B., Cook, B., and Doebbeling, B.N. Women's Military Environmental Risk Factors for Violence: Assessment by Era. Abstracts of the 15th Annual International Society for Traumatic Stress Studies Meeting, Miami, FL, November 14-17, 1999.

Sadler A., Booth, B., Cook, B., and Doebbeling, B.N. Repeated Violence Against Women During Military Service: Effects on Health Status and Outpatient Medical Utilization. Abstracts of the Community Prevention Research in Women's Health Conference, NIH, Bethesda, MD, Oct. 26-27, 2000.

Sadler A., Booth, B., Cook, B., and Doebbeling, B.N. The Military Environment: Risk Factors For Women's Non-Fatal Physical Assaults. Abstracts of the Community Prevention Research in Women's Health Conference, NIH, Bethesda, MD, Oct. 26-27, 2000.

Carney, C.P., Sampson, T.R., Voelker, M.D., Woolson, R.F., and Doebbeling, B.N. Women in Theater: The Gulf War Experience. Abstracts of the 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., January 24-26, 2001.

Sampson, T.R., Carney, C.P., Voelker, M.D., Woolson, R.F., and Doebbeling, B.N. Health Care Utilization & Disability of Gulf War Era Women. Abstracts of the 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., (oral), January 24-26, 2001.

Voelker, M.D., Woolson, R.F., Carney, C.P., Holman, J., Saag, K.G., Letuchy, E., and Doebbeling, B.N. Prospective Follow-up of Health Status in Gulf War Veterans and Era Controls. Abstracts of the 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., January 24-26, 2001.

Voelker, M.D., Saag, K.G., Schwartz, D.A., Chrischilles, E., Clarke, W.R., Woolson, R.F., and Doebbeling, B.N. Health-related Quality of Life in Gulf War Deployed and Era Military Personnel. Abstracts of the 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., January 24-26, 2001.

Barrash, J., Voelker, M.D., Woolson, R.F., Schumacher, A., Franciscus, C., and Doebbeling, B.N. *A Priori* Case Definition of Cognitive Dysfunction: The Iowa Gulf War Study. Abstracts of the 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., January 24-26, 2001.

Doebbeling, B.N., Voelker, M.D., Clarke, W.R., Torner, J.C., and Woolson, R.F. Health Services Utilization Five Years Post Gulf War. Abstracts of the 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., January 24-26, 2001.

Doebbeling, B.N., Sampson, T.R., Voelker, M.D., Carney, C.P., Woolson, R.F., Franciscus, C.J., Adams, M.M., and Holman, J.E. Registry Participation: Risk Factors and Postwar Morbidity. Abstracts of the 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., January 24-26, 2001.

Sadler A., Booth, B., Cook, B., and Doebbeling, B.N. The Military Environment: Risk Factors for Women's Non-Fatal Assaults. Selected Abstracts of the VA Health Services Research and Development 19th Annual Meeting, Washington, DC, (poster), February 14-16, 2001, Abstract #91, pages 130-131.

Sadler A., Booth, B., Cook, B., and Doebbeling, B.N. Repeated Violence Against Women During Military Service: Effects on Health Status, Outpatient Medical Utilization and Access to Care. Selected Abstracts of the VA Health Services Research and Development 19th Annual Meeting, Washington, DC, (oral), February 14-16, 2001, Abstract #143, pages 186-188.

Voelker, M.D., Woolson, R.F., Carney, C.P., Black, D.B. and Doebbeling, B.N. Self-reported use of mental health care by Gulf War veterans and era controls. NIMH Trainee Workshop, Academy for Health Services Research and Health Policy, Atlanta, June 10-12, 2001.

McGlasson DL, Harris MA, Brey RL, Holman JE, Woolson RF, Voelker MD and Doebbeling BN. Antiphospholipid antibodies in a blinded sample of Gulf War deployed and nondeployed military controls. Abstracts of the International Society of Thrombosis and Haemostasis Conference. Paris, France, July 6-12, 2001, Thrombosis and Haemostasis, Supplement July, 2001.

Sampson, T.R., Voelker, M.D., Carney, C.P., Woolson, R.F. and Doebbeling, B.N. Pre- and Peri-deployment Risk Factors for Participation in Gulf War Health Registries. Annual Meeting of the American Public Health Association, Atlanta, GA, (oral), October 22, 2001.

Other: Exhibits, Films, Tapes, Special Presentations:

Doebbeling, B.N. "The Iowa Persian Gulf Study: An Update," Institute of Medicine/National Academy of Sciences, Committee on the Health Effects Associated with Exposures Experienced During the Gulf War, Georgetown, June 14, 1999.

Doebbeling, B.N. "Case Definition Panel Discussion" Scientific Discussant, 4th Annual Meeting of Federal Investigators on Gulf War Illness, Washington, DC, June 23, 1999.

Doebbeling, B.N. "Veterans' Forum: A Roundtable Discussion," Scientific Discussant, 4th Annual Meeting of Federal Investigators on Gulf War Illness, Washington, DC, June 24, 1999.

Doebbeling, B.N., Voelker, M.D. "Illness Among Persian Gulf War Veterans", Invited Presentation, Iowa County Commission on Veterans' Affairs, Des Moines, Iowa, October 13, 1999.

Doebbeling, B.N. "Dissemination Workshop: Gulf War Veterans: Measuring Health and National Center for Military Deployment Health Research", Invited Panel Member, Institute of Medicine, National Academy of Sciences, Washington, D.C., December 16-17, 1999.

Doebbeling, B.N. "Health-Related Quality of Life in Gulf War Veterans," Invited Presentation, Persian Gulf Veterans Coordinating Board, Research Working Group, Washington, D.C., April 27, 2000.

Doebbeling, B.N. "The Iowa Cohort Study," in "Ongoing Longitudinal Follow-up Studies of Gulf War Veterans", Invited Plenary Speaker, 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., January 24-26, 2001.

Doebbeling, B.N. "The Iowa Study Syndrome Analysis" in "Is There a Gulf War Syndrome?: Alternate Approaches to Case-Definition", Invited Plenary Speaker, 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., January 24-26, 2001.

Barrash, J. "Results of Neuropsychological Research of Gulf War Veterans", Invited Plenary Speaker, 2001 Research Conference on Gulf War Veterans' Illnesses, *"Illnesses in Gulf War Veterans: A Decade of Scientific Research"*, Washington, D.C., January 24-26, 2001.

Doebbeling, B.N. "Longitudinal Gulf War Illness Studies: Boston, Iowa, UK and New Jersey", Invited Plenary Speaker, Military Veterans Health Coordinating Board Plenary Session, Rockville, M.D., December 10-12, 2001.

Papers Submitted:

Voelker MD, Saag KG, Schwartz DA, Chrischilles E, Clarke WR, Woolson RF, and Doebbeling BN. Health-related quality of life among Gulf War Era military personnel. *Am. J. of Epidemiol*, (submitted), 2001.

Barrett DH, Carney CP, Schwartz DA, Voelker MD, Falter K, Woolson RF, and Doebbeling BN. Post-traumatic stress disorder and physical health status among U.S. military personnel serving during the Gulf War period: A population-based study. *Psychosomatics* (in revision), 2001.

Barrett DH, Gray GC, Doebbeling BN, Clauw D and Reeves WC for the Persian Gulf Veterans Coordinating Board. The Prevalence of Symptoms and Symptom-Based Conditions among Gulf War Veterans: Current status of research findings. In: J.R. Feussner (ed), *Illnesses among Gulf War Veterans: A Decade of Scientific Research*. *Ann. Intern. Med.* (submitted), 2000.

Carney, C., Sampson, T.R., Voelker, M.D., Woolson, R.F., Thorne, P.S., and Doebbeling, B.N. Women in The Gulf War: Combat Experience, Exposures and Subsequent Health Care Utilization. *Mil. Med.* (Submitted), 2001.

Gerrity TR, Heller J, Brix K, and Doebbeling BN for the Persian Gulf Veterans Coordinating Board. The Kuwait Oil Well Fires: Exposure and Health Effects. In: J.R. Feussner (ed), *Illnesses among Gulf War Veterans: A Decade of Scientific Research*. *Ann. Intern. Med.* (submitted), 2000.

Lange, J.L., Schwartz, D.A., Doebbeling, B.N., Heller, J.M., and Thorne, P.S. Exposures to the Kuwait Oil Fires and their Association with Asthma and Bronchitis Among Gulf War Veterans. *Am. J. Publ. Health* (Submitted), 2001.

Simms LJ, Watson D, and Doebbeling BN. Confirmatory factor analyses of posttraumatic stress symptoms in deployed and non-deployed veterans of the Persian Gulf War. *Journal of Abnormal Psychology* (submitted), 2001.

Appendix F. Study Personnel

Principal Investigator:	Bradley Doebbeling, MD, MSc
Co-Investigators:	Joseph Barrash, PhD Donald Black, MD Caroline Carney, MD, MS Praful Kelkar, MD Paul Peloso, MD, MSc Kenneth Saag, MD, MSc Robert Woolson, PhD Thoru Yamada, MD
Study Coordinator:	John Holman, MA
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Database Manager:	Carrie Franciscus, BS
Data Analysts:	Tomoko Sampson, MPH Elena Letuchy, MS Kirk Bateman, BS Jon Yankey, MS
Physical Examiners:	Dina Janzen, MD Robert Zwicky, DO Bogdan Cherascu, MD Komal Jaipaul, MD Razvan Arsenescu, MD
Research Assistant (Neurocognitive evaluations):	Amy Schumacher, MS
Senior Student Research Assistant:	Jane Anderson
Student Research Assistants:	Ann Adams Jamie Hoff Chuck Tonelli

Note: Several additional investigators have been regular participants in the study group, making regular contributions to the study and participating out of personal or scientific interest. These include two of our consultants and multiple other investigators: Drs. David Watson, PhD, Psychology; James Torner, PhD, Epidemiology; Caroline Carney, MD, MS, Psychiatry/Internal Medicine; Bogdan Cherascu, MD, Internal Medicine; Brian Cook, DO, MS, Psychiatry; Arthur Hartz, MD, PhD, Family Medicine/Health Management and Policy; Sue Joslyn, PhD, Internal Medicine/Epidemiology; Toni Tripp-Reimer, RN, PhD, Nursing/Anthropology; Anne Sadler, RN, PhD, Psychology, Iowa City VAMC; Jay Sandlow, MD, Urology; Julia Seng, RN, ARNP, Nursing; Susan Zickmund, PhD, Internal Medicine/Program in Biomedical Ethics; Kathleen Janz, Sport, Health, Leisure and Physical Studies.

Appendix G. Eligible Subjects (based on the study's three *a priori* outcomes)

Potential Subjects for Cognitive Dysfunction Study

	Symptomatic	Not Symptomatic	Total
Exposed	290	999	1289
Not Exposed	99	1076	1175
Total	389	2075	2464

Potential Subjects for Depression Study

	Symptomatic	Not Symptomatic	Total
Exposed	225	1064	1289
Not Exposed	131	1044	1175
Total	356	2108	2464

Potential Subjects for Chronic Widespread Pain Study

	Symptomatic	Not Symptomatic	Missing	Total
Exposed	300	989		1289
Not Exposed	144	1030	1	1175
Total	444	2019		2464